

phase diagram was well reproduced by the atomistic simulation model. Importantly, under appropriate conditions the lipids were found to separate into two different liquid phases with clearly visible boundaries. The simulation data was used to analyse the driving forces for the formation of lipid domains, as well as their dynamics. In light of the results for this simple model system, we discuss how much can we expect to learn from related phenomena in more complex membrane systems.

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Extracting Structural and Mechanical Properties of Lipid Vesicles from Molecular Dynamics Simulations

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We have developed of a novel algorithm to determine both bending rigidity and membrane structure from molecular dynamics simulations of lipid vesicles. Using Spherical Harmonics (SH) analysis, we decompose the membrane fluctuations into a series of SH coefficients. These coefficients are used to construct the undulation power spectrum describing the intensity of undulations as a function of arc-length, similar to the method described by Brandt et al. 2011 for flat membrane geometries. The low wavenumber (large arc length) undulation modes provide a link to the continuum theory representation of membrane deformation, allowing us to extract bending rigidity. Furthermore, by applying a two-dimensional low-pass spatial filter to the SH coefficients (adapting a method developed by our group for flat-patch undulating bilayers, Braun et al. 2011), we can reconstruct the spherical undulating reference surface and extract accurate structural parameters for the lipid bilayer (e.g. membrane thickness and area-per-lipid). These new tools will be broadly useful for accurate analysis of future simulations investigating the effect of membrane insertions (such as cholesterol or proteins) on vesicle structure and mechanics.

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Molecular Dynamic Studies on Organelle-Specific Yeast Membrane Models and Amphipathic Lipid Packing Sensor Motif Binding Mechanism

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The present study analyzes improved computational membrane models for specific organelles in yeast. Previous molecular dynamic (MD) simulations were performed on yeast membrane models having six lipid types with lipid composition averages between the endoplasmic reticulum (ER) and the plasma membrane (PM) (*BJ* 97:50-58). The models studied in this research include ergosterol (ERG), phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylinositol (PI) lipids, with bilayer diversity ranging between six and eleven lipid types. MD simulations were used to equilibrate systems with lipid compositions characteristic to the ER, PM, and Golgi network (TGN) membranes. Data analysis provided better understanding of membrane behavior, mechanical properties, order parameters, electron density profiles (EDPs), and lipid packing. Selected models will be used to advance the study of peripheral membrane Osh4 binding mechanism and function. The ALPS-like motif, a peptide from Osh4, was previously identified in our lab as a recurring portion of the protein involved in the binding process (*JMB*243:847-862). The binding mechanism of ALPS to DOPC bilayers was studied with MD simulations of at least 200ns. All simulations were carried with the NPT ensemble, but simulations in the constant surface tension ensemble (NP γ T) were also run with the bilayer-peptide systems at varying values for γ .

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Molecular Dynamics Simulations of 4-Component Membranes with Novel Cationic Lipids Yield Insight into ApoE Binding

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Delivery of siRNA to the RISC complex for therapeutic effect remains a difficult challenge. One approach investigated by Merck is siRNA delivery via an artificial membrane. By encapsulating the siRNA in membrane, these so-called lipid nanoparticles (LNPs) are able to survive in plasma long enough to reach their target, e.g. liver cells. Multicomponent LNPs are investigated through large scale molecular dynamics (MD) simulations. Specific LNP formulations comprising cholesterol, phospholipids, PEG-lipid and a variety of cationic lipids have been studied. The MD simulations were carried out using

the GROMACS united atom potentials in the NPT ensemble with the temperature set at 310K. Each model LNP was simulated for ~ 150ns. These large simulations were accomplished with 128 processors on Merck's Cray-XT5 and the support of MRL IT. Average surface areas (SA), lipid conformations and lipid order parameters are calculated from steady state trajectories for each of the cationic lipids. Simulations results can be compared to experimental observables such as ApoE binding and fusogenicity, providing an atomistic level hypothesis of measured differences. For example, larger SA/lipid appears to correlate with stronger ApoE binding.

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What Did We Learn from Model Membrane Studies on Biological Membranes

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The use of models of some sort in order to understand certain aspects of biological systems is an established practice. Furthermore, quite often we argue in research proposals that "a study of a model helps understanding the much more complex biological system". This abstract presents a preliminary attempt to test the validity of the latter statement regarding the contribution of model membranes studies (particularly liposomes) to the understanding of various aspects of membrane biochemistry and biophysics. Whoever applied to a granting agency for support will testify that the issue is far from being trivial. An obvious example is the establishment of the lipid bilayer as the fundamental structure of all biological membranes.

The History of the controversy that existed before lipid bilayer emerged as the consensus structure, as described by Thompson and Henn in their comprehensive review in 1969 (in *Structure and Function of Membranes* In Mitochondria and Chloroplasts, ed. E. Racker, pp. 1-52, Reinhold N.Y.), shows that the resolution can be attributed to experimental studies on phospholipid bilayers.

Many more examples can be raised, including, the profound "condensing effect" of cholesterol on bilayer structure, first found by use of the simple, fundamental system and apparatus invented by Irving Langmuir, the understanding of the diffusion of proteins, impeded in real membranes by intermolecular interactions compared to models in which they move freely, the understanding of the causes for lateral phase separations and the development of novel lipofection agents based on studies of the role of cationic amphiphiles on PKC activity.

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Molecular-Level Organization of the Tear Film Lipid Layer: A Molecular Dynamics Simulation Study

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Tear film is essential to the health and optics of the human eye. It refreshes with every blink and ruptures if blinking is suppressed. Its instabilities lead to the dry eye syndrome. The outermost layer of the tear film consists of lipids which provide an optically smooth surface over the cornea and retard water evaporation. The tear film lipid layer formation and structure are still debated. We employ coarse grain molecular dynamics simulations to study molecular-level structure and dynamics of the tear film lipid layer. A novel, realistic tear film model under conditions mimicking those experienced by the tear film under physiological conditions was built and employed.

Simulations show that polar phospholipids separate their non-polar counterparts from the water phase, constituting a monomolecular uniform platform at which a thick non-polar lipid layer is formed. This lipid arrangement is stable upon lateral compression. A significant restructuring of the film occurs upon non-equilibrium lateral compression which mimics eye blinks. The water/lipid interface undulates, and lipids are sorted based on their head group size. Undulations of the water/lipid boundary are followed by transfer of some of polar lipids and water toward the non-polar phase, resulting in formation of inverse micelles in the non-polar lipid layer with water encapsulated by polar lipids. Moreover, some of non-polar lipids are transferred into the water phase in vesicles formed by polar lipids.

We predict that the tear film lipid layer at the molecular level is a dynamic and non-uniform assembly with lipids and water forming numerous three-dimensional structures in the vicinity of the lipid/water interface. These structures form and reorganize due to the action of eye lids during blinks. They may serve as lipid reservoirs and thus effectively increase stability of the tear film.